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Mr. Ian MacKay
Clinical Trials and Special Access Programme
Bureau of Pharmaceutical Assessment
Finance Building Tunney's Pasture
Address Locator: 0202A1
Ottawa, ON
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Dear Mr. MacKay,

The Canadian Forces vaccinated three main groups (576 persons total) with Anthrax Vaccine Adsorbed (AVA) from lot 020-1 during Operation Determination (approximately March – May 1998) in the Persian Gulf. There were 1676 doses of AVA administered. This summary of adverse event (AE) data will also be submitted to the manufacturer, BioPort Corporation of Lansing, Michigan. Individual AE reports are also enclosed for consideration if necessary by the LCDC Advisory Committee on Causality Assessment (ACCA).

The following points should be noted in interpreting this data:

a. only one, two, or three doses were administered to recipients before the operation ended, and the full six-dose series was not completed;

b. literature listing several different adverse event classifications or definitions were available at the time of the operation (manufacturer, US Army Medical Research Institute of Infectious Diseases, published studies). Medical Officers were therefore inconsistent in their initial adverse event classification. For the sake of comparability with the US Department of Defense (DoD) and manufacturer's data, clinical records and unit adverse event logs were reviewed by the attending medical staff and adverse events were categorised according to the manufacturer's classification system. Definitions used were:

1) local mild: erythema and tenderness/induration 1-5 cm diameter around injection site (expected - 30%);

2) local moderate: local inflammatory reaction >5cm diameter (expected - 4%);

3) local severe: edema of the forearm in addition to a local inflammatory reaction (expected <1%); and

4) systemic: chills and fever or malaise and lassitude, other systemic symptoms (expected 0.2%);

c. the manufacturer's expected rates are based on data from published studies and the US Vaccine Adverse Event Reporting System (VAERS). As you know, VAERS data are from passive surveillance and represent unverified reports temporally-associated with one or more vaccines. The data are subject to limitations of under-reporting, simultaneous administration of multiple vaccine antigens, reporting bias, and lack of incidence rates in unvaccinated comparison groups. Specifically for DoD-generated Anthrax vaccine AE data, any individual has been able to report any AE to VAERS directly, but DoD has previously only reported those which result in hospitalisation or loss of duty for over 24 hours (this is apparently similar to the ACCA AE inclusion criteria). Our report is, on the other hand, all-inclusive. Few AE were spontaneously reported, and most were identified through specific questioning of recipients by medical staff. Such active surveillance can be expected to result in rates up to 4.6 times higher than through passive surveillance (Thacher SB et al, 1986);

d. causality has yet to be assessed for these AE. One is considered serious and satisfies the DoD/VAERS reporting criteria, although it is doubtful that it will be assessed as being causally-related to the vaccine. Some are unexpected in that they are not specifically noted as expected AE by the manufacturer. Although baseline incidence rates for these unexpected symptoms have not been established, anecdotal observation in the Golan indicates that the baseline incidence of flu-like GI symptoms, headache, and foul taste (due to climate, living conditions, diet, and water quality) were similar to the post-vaccination rate. Anecdotal observation of heartburn symptoms among Canadian Forces members and rates of issue of over-the-counter antacids also suggest that the baseline incidence exceeds the total of two heartburn AE; and

e. the manufacturer and DoD have reported that nodules lasting up to two months may develop at the site of injection in up to 40-50% of recipients. The manufacturer does not include such nodules in the definition of an AE, but they are noted as possible accompaniments to other AEs. One recipient (listed as a mild local AE) reports a persistent nodule at the site of injection, and it will be excised in November 1999. He also subsequently identified additional nodules in his left leg, but excision pathology revealed these to be benign fibrous histiocytomas (dermatofibromas). No other long-term effects have otherwise been reported.

The following table is a summary of adverse events reported via active surveillance:

Classification	Number of AEs (% by dose)	Persons Reporting AEs (% by recipient)	Serious (VAERS-reportable) AEs (% by dose / % by recipient)
Local Mild	73 (4.36)	56 (12.67)	0
Local Moderate	4 (0.24)	3 (0.52)	0
Local Severe	0	0	0
Systemic	37 (2.21)	33 (5.73)	1 (0.17 / 0.06)
Total	113	91	

The Systemic events included the following:

Classification	Symptom	Number
Systemic	Headache	13
	Flu-like GI symptoms	9
	Fever	5
	Neurological	1
	Foul taste in mouth	3
	Heartburn	6 (2pers x 3 doses)

Attached are the nine Reports of a Vaccine-Associated Adverse Event submitted by the in-theatre Medical Officers and a copy of the manufacturer's product insert.

Questions may be directed to Lieutenant Colonel J-R Bernier ACOS Ops/Operational Medicine at (613) 945-6661 or Captain MC Lanouette ACOS Ops/Regulatory Affairs at (613) 945-6737.

Sincerely,

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Colonel
Assistant Chief of Staff Operations
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Enclosures: 10

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